REMARKS

Reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

By this Amendment, claim 22 had been amended, such amendment being fully supported in the as-filed specification.

The claims presently pending before the Examiner are 22-26, 28, 29 and 31-34.

Claim Rejections under 35 USC § 112

In the outstanding Office Action, the Examiner rejected claims 22-34 under 35USC 112, first paragraph, because the specification, while being enabling for implants having an extended overall release of the active principle which has a portion with a linear profile, does not reasonably provide enablement for implants having an extended overall release of the active principle with a linear profile. This rejection is traversed.

Applicants have amended claim 22 by clearly specifying that such implants have a limited initial release of the active principle and a subsequent linearly varying extended release thereof as supported by the as-filed specification and all the examples.

In view of this amendment, the rejection has been overcome and should be withdrawn.

Claim rejection: Double patenting of the Obviousness Type

The Examiner has rejected claims 22-25 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 9 of US patent No. 6,620,422 (Maquin et al.) in view of Chou et al. and Jain et al.

Specifically, the Examiner states that in view of Jain, it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the PLGA used in the drug core of the device from Maquin et al. in an outer skin from Chou et al to give additional control of the device release kinetics and reduce any burst that occurs.

Applicants strongly disagree with the Examiner's position and in support to the non-obviousness of the claimed invention hereby present the following argument.

As pointed out in Applicants' previous responses, the field of endeavor of Chou et al. is the reduction of the initial burst in the **sustained release** of drugs. In this regard, a number of polymers are listed as being suitable for achieving this object, as being supposedly usable in the core and the outer tube of a coextruded device. All of the hypothetical combinations are therefore considered by the Examiner to be equivalent in providing the presumed reduction of initial burst and the early achievement of a close to zero order release profile. In the Examiner's view, this renders the listed polymers definitely interchangeable among each other both in the core and in the coating, since in her estimation they are deemed to give the same technical effect.

However, the Examiner's conclusion is contradicted by the teaching of Chou et al. themselves, when the given examples, especially with reference to Fig. 2 and Fig. 3, show that PLGA and PCL do not provide for a similar profile. In addition, Chou et al. in paragraph [0065] (the same paragraph as cited in the Office Action, pages 11-12), last sentence, indicate that different polymers lead to variations in release rate, as well as different physical properties for extrusion, thus affecting the resulting delivery device differently.

Furthermore, it should also noted that, again in paragraph [0065], Chou et al. teach that the release rate of FA is proportional to the drug loading level in the matrix, thus meaning that the higher the drug loading, the higher the release rate, and so the shorter the overall release duration, according to the context of the sustained release devices.

Moreover, in the subsequent sentence, Chou et al. specify that "Compared to PLGA, EVA largely retarded the release of FA". This means that, not only different polymers have different release profiles, but also that EVA should be effectively considered as a coating when a very extensive retard of the drug release is desired.

The Examiner states at page 15 of the Office Action that "The Examiner does not dispute that Chou et al envision EVA as a possible coating polymer however, this does not negate that teachings of PLGA in this role". Applicants again strongly disagree

because if a teaching is present in Chou et al., it is not that EVA is "a possible coating polymer", but it is only the recommended polymer "when a very extensive retard of the drug released is desired". The subject of this rejection is obviousness and there is no teaching in Chou et al. which encourages the choice of PLGA as a coating polymer in order to have "a very extensive retard of the drug released."

Jain et al do not add any further teaching or suggestion to choose or select PLGA as a coating material "when a very extensive retard of the drug released is desired". The Examiner refers to Figures 2 and 4 in order to support her reasoning. First of all, in Figures 2 and 4, a release of 15 days is shown, which is a very short time, particularly if compared with Figures 3B, 4B, 5B, 6B, wherein the "linearly extended release" is after 14 days.

Furthermore, the actual teaching of Jain et al. is reported in the concluding paragraph entitled 4. Conclusion (p. 262), wherein it is stated that, "The in vitro drug release was enhanced with decrease in the PEG concentration and increase in the drug and mannitol concentration. The drug release was retarded with increase in the molecular weight of the encapsulated drug...". As a matter of fact, the use of PEG as a solution of the drug is essential according to Jain and this is the important tool to modify the release profile. There is no teaching or suggestion about covering a core containing the drug with PLGA, and hence there is absolutely no suggestion to the use of such a coating made of PLGA.

Last but not least, the Examiner does not identify the reason why one of ordinary skill in the art would have combined the teaching of Maquin et al. with Jain et al. In fact, the person of ordinary skill in the art would never have considered Jain et al. in order to extend the release when starting from an implant as stated in Maquin, which is the basis of the double patenting rejection.

Therefore, the claimed pending invention is **not obvious** over claims 1-3 of Maquin in view of Chou et al. and Jain et al, since in this prior art document, besides the number of instances of ***teaching away*** from the claimed invention, **there were neither suggestions nor motivations provided to search in the direction of the claimed**

invention, while conversely being led to modify the teaching of Chou et al. in the way at most including EVA in the coating.

In view of the foregoing arguments, the § 103(a) obviousness-type double patenting rejection has been overcome and should be withdrawn.

Claim Rejections under 35 USC § 103

Claims 22, 25 and 31, 32 have been rejected as being unpatentable over Chou et al. in view of Wang et al. This rejection is respectfully traversed.

The Examiner states that "Chou et al and Wang et al. teach polymeric drug cores coated with polymer, where both the core and coating polymer are the same and envisioned as PLGA", that Wang et al teach to utilize the 100,000 molecular weight 75/25 PLGA as the PLGA in the device of Chou et al, and concludes by stating "One having ordinary skill in the art would have had a reasonable expectation of success for this combination producing a release profile with a linear region since Wang et al. teach that a partially linear release profile is generated from their particular combination.". According to the Examiner this can be seen by Figure 2.

The Applicants strongly disagree with this reasoning.

As far as the Chou et al. document is concerned, Applicants underscore once again that Chou et al. do not suggest a coating comprising as the main component PLGA, because of the teaching that compared to PLGA, EVA largely retards the release of the active principle.

In any event, Wang et al. do not teach a partially linear release profile generated by the use of PLGA in the core and in the coating.

In fact, Wang et al. teach that the implants must have a ***hole drilled through the coating*** or ***even a hole drilled through the coating and the core*** in order to control the release of the active principle.

In Fig. 1 of the document (p. 1060), CM1 and CM2 are referred to as a drug/ matrix mix with a coating and with a hole only in the coating, and to a drug/ matrix mix

with a coating with a hole both in the core and in the coating, respectively. CT refers to the pure drug and MT to the sole core corresponding to the mix of drug and matrix.

In Fig. 2, to which the Examiner makes reference, typical release profiles are reported. All of the implants, MT, CT, CM1 and CM2 show a linear profile in less than one day, since this behaviour is independent of the coating. As a matter of fact, Fig. 2 shows that the release can be controlled, specifically a prolonged release can be attained by drilling a hole in the implant, which is more prolonged than one having a hole drilled through the coating on one side.

There is absolutely no disclosure in Wang et al. about obtaining a "linear profile" by combining the coating with the core where both are made of PLGA. As a matter of fact, the time is reported on the *x*-axis in hours. If the first five hours are considered and magnified, the drug/matrix mix also have a linear profile which confirms that no importance or significance is given to the coating. It should be underscored and noted by the Examiner that Wang et al. themselves confirm that it is the ***hole*** which has been drilled which is the ***crucial element to control the release.***

The Examiner states that the time duration that corresponds to "extended overall release" is not relevant to make the objection and therefore she does not consider that in Wang et al's. Figure 2 almost 100% of the drug in implant CM1 is delivered in less that one day. Applicants deem that the CM1 implant cannot be considered as providing a basis for a teaching of an "**extended** release" implant, but only for a "controlled release", as was discussed extensively in the state of the art of the instant specification.

Furthermore, it should also be noted that the coating of Wang et al., which is defined as impermeable, has been found to be intact at the end of the release study (see p. 1061, par. "In Vitro Release"). This is in marked contrast to the teaching of Chou et al., whose outer polymer skin should be bioerodible.

In this regard, it is clear that one of ordinary skill in the art would never have even considered combining the above teachings, since they are ***inconsistent with each other.***

Since the claims distinguish over the combination of references by a preponderance of the evidence, the § 103(a) rejection has been overcome for failure to

establish a case of *prima facie* obviousness. Withdrawal of the rejection is, accordingly, respectfully solicited.

Claim Rejections -35 USC § 103

Claims 22-23, 26 and 28-29 have been rejected as being unpatentable over Chou et al. in view of Wang et al. and in view of Jain et al. and Sakamoto et al. This rejection is respectfully traversed.

The Examiner bases her reasoning on the assumption that "Chou et al. in view of Wang et al. make obvious the composition of claim 22 where the inclusion of an outer coating reduces the burst release of the contained drug and linearizes the release profile".

Applicants refer to the above paragraph to support their position that not only do Wang et al. not teach the linear profile as being due to the use of a core and coating, both of which are made of PLGA, but also to the fact that one of ordinary skill in the art would not have thought to combine Wang et al. with Chou et al.

At any rate, the citation of Jain et al in combination with Sakamato to teach the inclusion of a hydrophilic excipient in a PLGA matrix, as in the claimed invention, appears to Applicants to be contradictory.

As a matter of fact, Jain et al. do not teach the use mannitol in order to have a retard in the *in vivo* drug release. This is clearly shown in Figure 4, wherein it can be seen that a more prolonged release occurs for PLGA microspheres ***without mannitol***.

According to the present invention, as disclosed at paragraph [0106] and shown in Figure 11, the coating having added to the PLGA at least one hydrophilic excipient, allows the obtention of a fairly constant release rate for a more extended period of time.

Therefore, the skilled person in view of Jain et al in combination with Sakamoto would never have added mannitol to the Chou et al implant because this addition would have resulted in a ***faster release,*** as shown in Figure 4 of Jain et al.

Since the claims distinguish over the teachings of the combination of references, the § 103(a) rejection has been overcome and should be withdrawn.

Claim Rejections under 35 USC § 103

Claims 22 and 33-34 are rejected under 35 USC 103(a) as being unpatentable over Chou et al. in view of Wang et al as applied to claims 22, 25 and 31-32 above and further in view of Fujioka et al. This rejection is respectfully traversed.

The Examiner bases her reasoning on the assumption that "Chou et al. in view of Wang et al. make obvious the composition of claim 22 where the inclusion of an outer coating reduces the burst release of the contained drug and linearizes the release profile".

Applicants refer to the above paragraph to support their position that not only do Wang et al. not teach the linear profile as being due to the use of core and coating, both made of PLGA, but also to the fact that the skilled person would not have combined Wang with Chou.

In any event, Fujioka et al refers to a controlled release device, which is ***not*** of a matrix-type drug formulation and, therefore, one of ordinary skill in the art would never have even considered combining it with Wang et al. and Chou et al., both of which undoubtedly refer only to matrix-type drug formulation.

Specifically under the summary of the invention in Fujioka et al., it is stated:

> Unlike the previous matrix-type drug formulations, in which water can infiltrate without any restriction into the interior of the drug formulation across the entire surface immediately upon contact with an aqueous medium, the rate of water infiltration is subjected to an optimal regulation in the drug formulation of the present invention. This functions to circumvent the problems described above, even for devices with small diameters, and makes it possible to achieve long-term zero-order release. Thus, the present invention facilitates development of practical drug formulations that combine two features: (i) simple, nonsurgical administration using an injector-type instrument, and (ii) the ability to maintain long-term efficacy.

The ability to maintain long-term efficacy is in fact guaranteed by an implantable rod-like drug formulation comprising (a) a nondisintegrating inner layer comprised of a biocompatible material that contains a uniformly dispersed water-soluble drug; and (b) an outer layer comprised of a biocompatible material wherein said outer layer surrounds the circumference of the inner layer and said outer layer is impermeable to water and is

capable of controlling the swelling of the inner layer; wherein the ratio of the axial length of the drug formulation to the cross-sectional diameter of the inner layer is one or more and one or both ends of the inner layer are open so as to come into direct contact with the intracorporeal environment.

One of ordinary skill in the art would have never used the teaching of Fujioka et al. which disclose an impermeable outer layer in combination with Chou et al., which provides for an bioerodible outer skin, since the ***respective teachings are inconsistent*** with each other.

Furthermore, by referring to the Declaration by Mr. Mauriac filed March 27, 2009, in a matrix-type drug formulation according to present claim 22, when a drug/PLGA composition is placed in an aqueous environment, water diffuses into the matrix to form domains of aqueous drug solution. Water in contact with polyester chains of PLGA allows for hydrolysis of the ester bonds to occur. This hydrolysis releases acidic residues which, if they remain in the close surroundings of the ester bonds, will help in causing a further hydrolysis to occur, thus promoting a kind of autocatalysis. The overall release duration of the claimed PLGA-based implants depends on the time at which the polymeric matrix will fully degrade. A relatively low release rate, leading to an early matrix degradation, will result in a relatively short overall release duration.

The foregoing summary of Mr. Mauriac's Declaration clearly excludes the Fujioka et al. patent as containing any disclosure which can be said to render obvious any feature of the claimed invention when combined with Chou et al. and Wang et al.

Since the claims clearly distinguish over the combination of references, the § 103(a) rejection has been overcome and should be withdrawn.

Claim Rejections under 35 USC § 103

The Examiner has rejected claims 22-25 under 35 USC § 103(a) as being unpatentable over Maquin et al in view of Chou et al. and Jain et al. This rejection is traversed.

This rejection is identical in its reasoning to the double patenting rejection which was responded to above.

The arguments set forth above in response to the obviousness-type double patenting rejection are incorporated herein by reference. Since the rejection has been overcome, its withdrawal is respectfully solicited.

Applicants respectfully submit that having overcome all of the rejections of record, the issuance of a Notice of Allowance is in order and is solicited.

Please charge any fees which may be due and which have not been submitted herewith to our Deposit Account No. 01-0035.

Respectfully submitted,

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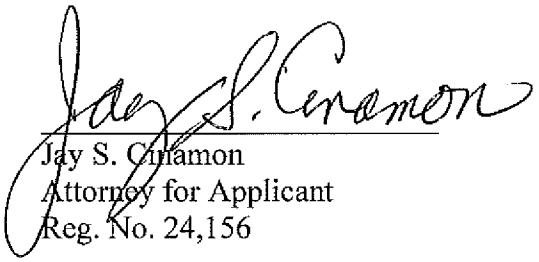
By 
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